Effect of Preoperative *Aspirin* Replacement With *Enoxaparin* in Patients Undergoing Primary Isolated On-Pump Coronary Artery Bypass Grafting

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Management of preoperative antiplatelet therapy in coronary artery bypass grafting (CABG) is variable among surgeons: guidelines collide with prejudices because replacement of aspirin with low-molecular-weight heparin is still performed because of a presumed minor bleeding risk. This study aims to analyze postoperative bleedings and complications in patients scheduled for elective primary isolated on-pump CABG, depending on preoperative aspirin treatment or its replacement with enoxaparin. In this cohort study, we propensity score matched 200 patients in whom aspirin was stopped at least 5 days before CABG and replaced with enoxaparin and 200 patients who continued aspirin therapy until the day before surgery. Postoperative bleedings and complications were monitored during hospitalization. Among patients who continued aspirin treatment, mean overall bleeding was 701.0 ± 334.6 ml, whereas in the matched enoxaparin group, it was significantly greater (882.6 ± 64.6 ml, p value <0.001); this was associated with reduced postoperative complications, lower values of postoperative C-reactive protein in aspirin takers, and a presumed protective effect for statins. After propensity score adjustment, aspirin treatment carried a protective effect against major postoperative bleeding (odds ratio 0.312, p = 0.001). In conclusion, postoperative bleeding is reduced in patients who continued aspirin, likely due to a reduction in postoperative inflammation. The practice of empirically discontinuing aspirin and replacing it with enoxaparin before CABG should be abandoned. Patients with coronary artery disease referred to CABG should continue antiplatelet medications until the surgical procedure. Those results might be extended to patients under oral anticoagulant therapy requiring CABG. **© 2016 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2016;117:563−570)**

Coronary artery bypass grafting (CABG) surgery aims to reduce early and long-term risk of myocardial infarction and death in patients with significant coronary artery disease. The continuation of aspirin therapy in patients who undergo coronary surgery, although potentially responsible of intraoperative and postoperative bleedings, can reduce postoperative myocardial infarction, improve oxygenation, and increase survival.[1] Furthermore, platelet inhibition has been shown to reduce the rates of acute bypass graft occlusion in patients undergoing CABG.[2] The problem of bleeding risk usually afflicts cardiac surgeons, and a systematic review concluded that aspirin is associated with an increased risk of postoperative bleeding and greater need for blood products.[3] Therefore, aspirin might be replaced 5 to 7 days before surgery with low-molecular-weight heparin enoxaparin, which exerts its action over 12 to 24 hours, is more easily manageable than unfractionated heparin, and is presumed to be associated with reduced bleeding compared with aspirin because platelet function is not impaired.[4] Although a recent systematic review of recommendations for preoperative antiplatelet discontinuation is remarking that enoxaparin is unable to protect from major cardiac events when used as replacement therapy before surgery,[5] the practice of replacing aspirin with enoxaparin is still in use in many centers worldwide relying more on surgeon's discretion and concern about intraoperative bleeding rather than scientific evidences or specific randomized clinical trials. Considering the lack of specific reports in this topic, the purpose of this study was to analyze the postoperative bleeding depending on aspirin or enoxaparin therapy in patients scheduled for on-pump CABG and, secondly, to demonstrate a correlation between preoperative aspirin or enoxaparin treatment and postoperative cardiac events.

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Each author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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See page 569 for disclosure information.

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Table 1
Preoperative evaluation

Variable	Enoxaparin replacement (n = 200)	Aspirin treatment (n = 200)	P value
Age (years)	68.1±9.4	67.8±9.9	0.734
Men	165 (82.5%)	165 (82.5%)	1.000
Hypertension	193 (96.5%)	198 (99.0%)	0.175
Diabetes mellitus	84 (42.0%)	73 (36.5%)	0.306
Insulin therapy	39 (19.5%)	50 (25.0%)	0.229
Smoker	52 (26.0%)	39 (19.5%)	0.152
Past-smoker	84 (42.0%)	88 (44.0%)	0.762
Statins therapy	155 (77.5%)	140 (70%)	0.111
Atorvastatin	114 (57.0%)	100 (50.0%)	
Simvastatin	22 (11.0%)	28 (14.0%)	
Rosuvastatin	15 (7.5%)	9 (4.5%)	
Others	4 (2.0%)	3 (1.5%)	
Statins: average dosage (mg)	40.2 (36.7 − 43.7)	43.3 (39.4 − 47.1)	0.212
Bronchodilators	10 (5.0%)	5 (2.5%)	0.292
Previous percutaneous transluminal coronary angioplasty	36 (18.0%)	45 (22.5%)	0.320
Extracardiac arteriopathy	55 (27.5%)	70 (35.0%)	0.131
Recent acute coronary syndrome	64 (32.0%)	63 (31.5%)	1.000
Previous acute coronary syndrome	39 (19.5%)	37 (18.5%)	0.899
Body mass index (kg/m^2)	26.8±3.2	26.9±3.6	0.753
Body mass index > 30 kg/m^2	37 (18.5%)	32 (16.0%)	0.597
Creatinine clearance (mL/min)	82.1±26.7	83.3±30.6	0.670
Preoperative ejection fraction (%)	54.5±7.2	55.1±6.2	0.408
Ejection fraction < 35%	10 (5.0%)	6 (3.0%)	0.445
Preoperative haemoglobin (g/dL)	13.5 (13.3 − 13.7)	13.5 (13.2 − 13.7)	0.989
Preoperative haematocrit (%)	40.5 (39.9 − 41.0)	40.3 (39.7 − 40.9)	0.738
Preoperative platelet count (/mm^3)	213 000(205000-222000)	211 000(203000-218000)	0.857
Creatinine (mg/dL)	0.96 (0.93 − 1.00)	0.99 (0.95 − 1.04)	0.544
International normalized ratio (INR)	1.09 (0.98 − 1.20)	1.02 (1.01 − 1.03)	0.564
Partial thromboplastin time (PTT) (s)	30.7 (29.8 − 31.6)	30.9 (30.0 − 31.7)	0.300
Fibrinogen (mg/dL)	369.7(354.8 − 384.6)	367.5(354.6 − 380.4)	0.807
C reactive protein (mg/L)	8.6 (5.9 − 11.3)	9.5 (6.5 − 12.5)	0.313
White blood cell count (10^9/L)	7.4 (7.1 − 7.7)	7.4 (7.1 − 7.7)	0.948
Troponin I (ng/L)	0.3 (0.1 − 0.4)	0.5 (0.3 − 0.7)	0.435

Methods

This study is based on a propensity score−matched evaluated cohort of consecutive patients who underwent elective primary isolated CABG at our institution (Department of Cardiovascular Surgery, Università Campus Bio-Medico di Roma, Rome, Italy) and treated with aspirin or enoxaparin preoperatively. The primary aim of the study was to analyze postoperative overall bleeding depending on preoperative antiplatelet therapy with aspirin or its replacement with enoxaparin. Secondary aims were the evaluation of postoperative complications in the 2 treatment groups and the possible role of statins in postoperative bleeding and complications.

Data generated by Kamran et al[6] have been used to estimate the sample size, although this calculation is generally used for randomized controlled trials. Considering an expected overall bleeding of 604 ± 348 ml for patients who continued aspirin until surgery, to detect a 20% positive difference assuming 2-sided 5% significance level at 80% power, 131 patients were needed in each group. This number was increased to a recruitment target of 200 patients per group assuming up to 50% noncompliance with the study protocol (such as missing variables) or unexpected variability because this was a cohort study and confounding variables are more difficult to be completely evaluated compared to a randomized clinical trial design. Approval of the study was obtained from the institutional review board.

We considered eligible for our study only patients in whom aspirin therapy (100 mg/day) was stopped at least 5 days before surgery and replaced with subcutaneous enoxaparin (100 IU/kg twice daily) until the day before surgery and patients in whom aspirin therapy (100 mg/day) was continued until the day before surgery. Preoperative treatment was left to surgeon's discretion. All patients were given their first oral dose of aspirin (100 mg/day) after about 12 to 24 hours from surgical procedure.[7]

Patients in anticoagulation, for example, due to mechanical heart valve or atrial fibrillation, were excluded from the study; also, we excluded patients who received ticlopidine, patients with a history of bleeding disorders, or patients with significant gastrointestinal bleedings for chronic liver failure. Redo cardiac surgery or off-pump coronary surgery were also exclusion criteria. Patients with a known history of systemic inflammatory diseases,

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